REMARKS

The Office Action and the cited and applied references have been carefully studied. Claims 301-316 are allowed. Claims 221-279, 305, 306, 309-316, and 332-334 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Among the amendments to the claims, the SEQ ID NOs in claims 242 and 276 are now amended based on the disclosures in the Examples of the specification as follows:

Subpart of claim	SEQ ID NO	Example
a)	43-36 136, 137 140-142 153-161 173, 174 202, 203 219, 220	9 17 18 19, 22 19 37 42
b)	148, 149 208, 209 211, 212	18 39 40
c)	205, 206	38
d)	185, 186	32
e)	190, 191 227, 228 289, 290	34, 44, 52
f)	225, 226	43
g)	244, 245 248-251 283, 284	46, 48, 51
h)	246, 247	46

Claims 238 and 315 have been objected to because of informalities. Appropriate corrections are made to claims 238 and 315, as well as to claims 311, 313, 314 and 316 in which the word "consisting" was misspelled.

Claim 223 is objected to as failing to further limit claim 221. The examiner states that a lack of distinction between substantially homologous and complementary fails to further limit claim 223. This objection is respectfully traversed.

Claim 223 which is dependent from claim 221 is now amended to recite "wherein the reaction mixture further contains [~~a~~] another chimeric oligonucleotide primer having a sequence substantially homologous to the nucleotide sequence of the nucleic acid as the template" in order to define the claimed invention more clearly. Claim 223 clearly recites that the reaction mixture additionally contains a chimeric oligonucleotide primer that is different from the chimeric oligonucleotide primer as recited in claim 221.

According to amended claim 223, the reaction mixture contains a chimeric oligonucleotide primer that is substantially complementary to the nucleotide sequence of the nucleic acid as the template as recited in claim 221 and, in addition, another chimeric oligonucleotide primer having a sequence substantially

homologous to the nucleotide sequence of the nucleic acid as the template. Those skilled in the art would readily understand that the former anneals to the nucleic acid as the template, while the latter anneals to the strand complementary to the nucleic acid as the template, and that these chimeric oligonucleotide primers are different from each other. This is illustrated in Figure 33.

If the nucleic acid as the template as recited in claim 221 is the upper strand of the "template DNA" illustrated in the upper part of Figure 33, the strand complementary to the nucleic acid as the template is the lower strand. The primer illustrated as a short line on the right of the middle part corresponds to the chimeric oligonucleotide primer that is substantially complementary to the nucleotide sequence of the nucleic acid as the template as recited in claim 221, while the primer illustrated as a short line on the left corresponds to another chimeric oligonucleotide primer having a sequence substantially homologous to the nucleotide sequence of the nucleic acid as the template as recited in claim 223. Thus, "substantially homologous" is clearly distinct from "complementary", and it is clear that claim 223 further limits claim 221.

Reconsideration and withdrawal of the objections are therefore respectfully requested.

Claims 298 and 301 have been objected to under 37 CFR 1.75 as being substantial duplicates of claims 305 and 307 and

claim 306, respectively. This objection is obviated by the cancellation of claims 298 and 301.

Claims 221-278 and 300 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claim 300 is cancelled and replaced with new claim 333, which is dependent from claim 305. In new claim 333, it is clearly recited that "the DNA polymerase in step (a) is different from the DNA polymerase having a strand displacement activity in step (c)", thereby obviating this part of the rejection.

Claims 221-278 are considered by the examiner to be rendered indefinite by a deficiency in an adequate number of active steps. The examiner states that it is unclear what steps occur in the mixture. While the claims recite that DNA polymerase has strand displacement activity and that endonuclease cleaves, the examiner indicates that it is unclear whether such enzymes would function to have the strand displacement and cleavage in the claims, nor is it clear as to what order the steps are to occur. This part of the rejection is respectfully traversed.

Claim 221 is now amended to recite "(b) incubating the reaction mixture for sufficient time to generate a reaction product under conditions where specific annealing of the primer to the nucleic acid as the template, an extended strand synthesis reaction and a strand displacement reaction by the DNA

polymerase, and a reaction of cleaving the extended strand by the endonuclease take place.

The amendments are supported by the following disclosures in the specification:

> The method of the present invention can be conducted by using at least one oligonucleotide primer as described above in (1) in combination with the endonuclease as described above in (2) and the DNA polymerase as described above in (3) (page 87, line 22 to page 88, line 1);
>
> A chimeric oligonucleotide primer used in the method of the present invention is a chimeric oligonucleotide primer that has a nucleotide sequence substantially complementary to a part of the nucleotide sequence of a nucleic acid as a template. It can contribute to extension of a DNA strand under conditions used. Furthermore, a ribonucleotide is positioned at the 3'-terminus or on the 3'-terminal side of the chimeric oligonucleotide primer (page 72, lines 11 to 19);
>
> Any endonuclease that can act on a double-stranded DNA generated by DNA extension from the chimeric oligonucleotide primer as described above in (1) that has been annealed to a nucleic acid as a template and cleaves the extended strand to effect a strand displacement reaction may be used in the present invention (page 78, line 24 to page 79, line 4);
>
> A DNA polymerase having a strand displacement activity on a DNA can be used in the present invention (page 8 1, lines 10 to 11); and
>
> The DNA polymerase used in the present invention should synthesize an extended strand from the 3'-terminus of the primer portion towards the downstream while

displacing a previously extended DNA strand (page 109, lines 16 to 19).

In step (a) of the method defined by claim 221, a reaction mixture is prepared by mixing a nucleic acid as a template, a deoxyribonucleotide triphosphate, a DNA polymerase having a strand displacement activity, at least one primer and an endonuclease that cleaves an extended strand generated from the primer, wherein the primer is a chimeric oligonucleotide primer that is substantially complementary to the nucleotide sequence of the nucleic acid as the template and contains a ribonucleotide as well as at least one selected from the group consisting of a deoxyribonucleotide and a nucleotide analog, the ribonucleotide being positioned at the 3'-terminus or on the 3'-terminal side of the primer.

Then in step (b), the reaction mixture is incubated for a sufficient time to generate a reaction product under conditions where specific annealing of the primer to the nucleic acid as the template, an extended strand synthesis reaction and a strand displacement reaction by the DNA polymerase, and a reaction of cleaving the extended strand by the endonuclease take place.

As a result, specific annealing of the primer to the nucleic acid as the template, an extended strand synthesis reaction and a strand displacement reaction by the DNA polymerase, and a reaction of cleaving the extended strand by the endonuclease take place in parallel in the reaction mixture, and

consequently the nucleic acid is amplified. As claim 221 specifically and clearly defines that these reactions take place in the reaction mixture, claim 221 and claims dependent therefrom are not indefinite.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 221, 223, 225, 226, 277, 278 and 298-300 have been rejected under 35 U.S.C. §102(b) as being anticipated by Walder et al. (EP 04964883 A2). The examiner states that Walder teaches a method of amplifying by preparing a mixture with template, dNTPs, DNA polymerase with strand displacement activity and endonuclease that cleaves extended strand and chimeric primer that is substantially complementary to nucleotide sequence and contains a ribonucleotide on 3'-terminal side and dNTP and incubating. The examiner further states that Walder teaches Rnase H. However, the examiner indicates that the claims do not read on the active steps of strand displacement. This rejection is respectfully traversed.

Walder discloses a process for decreasing contamination by an amplified product in nucleic acid amplification reactions, where the process comprises using a primer or polynucleotide substrate which contains a ribose residue in the amplification reaction; and cleaving the ribonucleotide linkage within the amplified product (see claim 1 of Walder). According to the

Walder's process, the carry-over problem is eliminated by employing novel RNA containing primer for the amplification reaction which can be cleaved from the product, and the cleavage of the primer at the ribonucleotide linkage interferes with further amplification (see page 3, lines 1 to 3 of Walder). The process can be carried out immediately following PCR, or the process can be performed prior to amplification (see page 4, lines 31 to 34 of Walder).

It is however clear that, in Walder, it is not intended that the ribonucleotide linkage in the primer is cleaved during amplification. If the cleavage does take place during amplification, an amplified product cannot be obtained because the cleavage interferes with further amplification.

By contrast, the presently claimed method comprises (b) incubating the reaction mixture which contains the chimeric ohgonucleotide primer for a sufficient time to generate a reaction product under conditions where specific annealing of the primer to the nucleic acid as the template, an extended strand synthesis reaction and a strand displacement reaction by the DNA polymerase, and a reaction of cleaving the extended strand by the endonuclease take place. As discussed in the indefiniteness rejection above, the reactions take place in parallel. Therefore, as the presently claimed method is quite different

from the process of Walder, claim 221 and claims dependent therefrom cannot be anticipated by Walder.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claim 317 has been rejected under 35 U.S.C. §102(e) as being anticipated by Kurn, U.S. Patent 6,251,639. This rejection is made moot by the cancellation of rejected claim 317 without prejudice.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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